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Chapter 7

Allogeneic transplantation after reduced intensity conditioning with fludarabine-cyclophosphamide for both indolent and aggressive lymphoid malignancies.

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Abstract

We studied outcome of allo-SCT after reduced intensity conditioning in relapsed or refractory indolent and aggressive lymphoid malignancies. All 54 patients (diagnosis: B-CLL n=13, indolent lymphoma n=12, aggressive lymphoma n=13, transformed lymphoma n=16) received conditioning with fludarabine and cyclophosphamide between July 2001 and November 2010. They underwent allo-SCT because of relapse after auto-SCT or because no other therapy could lead to a meaningful remission. Patients received an unmanipulated peripheral blood stem-cell graft.
Median follow-up was 67 months.Thirty-two patients had received rituximab.
Immediately after transplantation remission status had improved in 21 patients, all without DLI. During follow up six additional patients achieved CR without further therapy.
4-year OS (EFS) was 46% (46%) for B-CLL, 83% (75%) for indolent lymphoma, 69% (55%) for aggressive lymphoma and 74% (67%) for transformed lymphoma (p=0.28 (p=0,54)). 42% developed acute GvHD, 68% chronic GvHD (16% limited, 52% extensive). Previous auto-SCT did not influence OS, while acute GvHD did. Two year non-relapse mortality was 16%.
In conclusion, reduced intensity conditioning with fludarabine-cyclophosphamide is feasible and effective for both indolent and aggressive lymphoid malignancies, even after previous auto-SCT. Due to the excellent anti-B-cell/lymphoma activity fludarabine-cyclophosphamide decreases tumor load, gaining time for the development of a graft versus lymphoma effect.

Introduction

Allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment in case of relapsed lymphoid malignancies. However, myeloablative conditioning is associated with considerable treatment related mortality (TRM) and morbidity, which may be as high as 40%-70% (1,2). To improve upon these results and to expand accessibility of this procedure to older and more unfit patients, reduced intensity conditioning was introduced (3-5). Results were similar or even better as compared to myeloablative conditioning, mainly due to a lower TRM. However, as may be expected, relapse rates were higher than following myeloablative conditioning (6,7). It was also questioned whether reduced intensity condition would be appropriate for aggressive lymphoma's since, due to the kinetics of the disease, these regimens may be less able to control the disease until the graft versus lymphoma can exert its effect (8). Nevertheless, several small series have been reported, describing the potentially curative potential of reduced intensity allo-SCT even in aggressive lymphoma's (9,10). To further assess the role of this treatment modality, we reviewed outcomes of 54 patients with relapsed or refractory indolent as well as aggressive lymphoid malignancies, who received allo-SCT following reduced intensity conditioning in our center. The conditioning regimen consisted of a combination of fludarabine and cyclophosphamide which, as has been shown in other studies, produced only short-term myelosuppression and demonstrated good engraftment while, because T-cell depletion was not performed, retaining the graft versus lymphoma (GvL) effect (11). The patient group reported here is heterogeneous with respect to lymphoma type and previous treatments, however, all patients had at least stable disease at time of transplantation.

Patients and Methods

Patients

All patients who received alloSCT after reduced-intensity conditioning with fludarabine and cyclophosphamide for lymphoid malignancies between July 2001 and November 2010 at the VU University medical center (VUmc) were reviewed. Allo-SCT was indicated because of relapse after autologous stem cell transplantation (auto-SCT) or because no further therapy was expected to lead to cure or a meaningful remission.

Because only two patients with Hodgkin's lymphoma were transplanted, both were excluded from further analysis. Until 2008, only sibling allo-SCTs were performed.

After 2008, unrelated donor transplants were also performed. All donors were fully HLA (high resolution 10/10) matched.

Conditioning regimen and prophylaxis against graft versus host disease (GvHD).
The conditioning regimen consisted of fludarabine 25 mg/m^2 once daily i.v. and cyclophosphamide 500 mg/m^2 once daily i.v., both from day -7 until -3. On the day of transplantation (day 0), patients received an unmanipulated peripheral blood stem cell graft, targeting at a minimum of 4.0x10^6 CD34+ cells/kg patient body weight.
GvHD-prophylaxis consisted of ciclosporine (120 days, then taper 10% per week) and methotrexate (15 mg/m^2 once daily at days 1, 3 and 6 respectively) from July 2001 until October 2004 or ciclosporine (same schedule as above) and mycophenolate mofetil (MMF, 84 days) as of October 2004. GvHD profylaxis was terminated earlier in case of non-satisfactory donor chimerism or disease progression. In case of previous GVHD, ciclosporine tapering was at a rate of 5% per week. All patients received antibiotic prophylaxis consisting of ciprofloxacin 500 mg b.i.d. and fluconazole 50 mg q.d. until ANC>0.5x10^9/l and co-trimoxazole 480 mg q.d. plus feneticillin 250 mg q.i.d for 1 year. Herpes simplex and zoster prophylaxis consisted of valaciclovir 500 mg b.i.d. for one year. Prophylaxis was continued for a longer time in case of ongoing chronic GvHD.

End points/objective
The objective of this study was to assess overall survival (OS) and event-free survival (EFS) Secondary end points were relapse rate, non relapse mortality (NRM) and cumulative incidence of acute and chronic GvHD.
Acute GvHD was rated as occurrence of GvHD within 100 days after allo-SCT, and graded as described by Przepiorka (12). Chronic GvHD was defined by the revised Seattle-criteria, in which chronic GvHD is separated into a limited and extensive form (13).

Statistical analysis
Data were collected using retrospective chart and database review and analyzed using the SPSS statistical package (version 20.0). Overall survival (OS) and event free survival (EFS) were estimated using the Kaplan Meier method and compared using the log rank test.
OS was calculated as the time between date of allo-SCT and death, or patients were censored at last follow-up. EFS was calculated as the time between date of allo-SCT and the first relapse or progression or death of any cause.
With the use of univariate analysis (log rank test) the following possible prognostic factors were analyzed: age, diagnosis groups, time from diagnosis until transplant,

previous treatments, previous auto-SCT, disease status at time of transplant, CMV mismatch, ABO mismatch, sex mismatch (donor female, recipient male), acute and/or chronic graft versus host disease, previous rituximab treatment or not.

Results

A total of 54 patients (median age 53 years, range 36-68) were treated with allo-SCT after conditioning with fludarabine and cyclophosphamide between July 2001 and November 2010. All patients were transplanted with an HLA-compatible sibling except two (1 B cell chronic lymphocytic leukemia (B-CLL), one diffuse large B cell lymphoma (DLBCL)), who were transplanted with a 10-10 matched unrelated donor.
Median follow-up of all patients was 53 months, (range 2-130 months). Median follow up of all patients alive at last follow up is 67 months (range 19-130 months).
Patients were diagnosed with B-CLL (n=13), indolent B cell lymphoma (n=12), aggressive lymphoma (n=13) and 16 had DLBCL classified as transformation of indolent lymphoma (previous diagnosis of indolent lymphoma, now diagnosed with DLBCL). For more detailed patient characteristics see Table 1.
Patients received a median of three lines of therapy before allo-SCT, including re-induction therapy, and 16 patients (29%) had previously been treated with auto-SCT (5 indolent lymphoma's, 9 aggressive lymphoma's, 2 transformed lymphoma's).

Table 1: patient characteristics and transplant outcome

Disease	CLL (n=13)	Indolent B cell NHL (n=12)		Aggressive NHL (n=13)		Transformed NHL	
Disease subcategories		FL	n=8	DLBCL	n=4	TFL	n=15
		LPL	n=4	T-NHL	n=5	Richter	n=1
				MCL	n=4		
Median age (range)	55 yrs (46-68)	48 yrs (36-64)		54 yrs (37-64)		53 yrs (37-66)	
Male/female	12/1	6/6		11/2		10/6	
Treatment lines Median (range)	3 (2-4)	3 (2-5)		3 (1-5)		3 (1-4)	
Auto-SCT	0	5		9		2	
Acute GvHD	7	4		5		5	
Chronic GvHD	9	7		5		11	
extensive	8	6		4		6	
DLI	1	2		0		3	
Relapse/progression	2	2		5		2	
alive	6	10		9		11	
Cause of death							
infection	2			2			
relapse	1	1		2		2	
GvHD	4	1				2	
other						1	

CLL=chronic lymphocytic leukemia, FL=follicular lymphoma, LPL=lymphoplasmocytic lymphoma, NHL = non Hodgkin's lymphoma, DLBCL = diffuse large B cell lymphoma, MCL=mantle cell lymphoma, TFL =transformed lymphoma, GvHD=graft versus host disease, DLI=donor lymphocyte infusion.

Median time from autologous to allogeneic transplant was 38 months (range 11-96 months).

Twenty-two patients never received rituximab in the course of their disease, whereas 32 did receive rituximab, mostly in the last year(s) before transplant.

Engraftment, chimerism and donor lymphocyte infusions

All patients achieved complete donor chimerism at one year after transplantation, except two, who never achieved remission and eventually progressed. Median time to neutrophil recovery (>0.5 x 10.9/l) was 19 days (range 7-51 days). No early or late graft failures occurred. In nine patients, immune suppression was stopped prematurely at about two months post-transplant, because of incomplete and/or decreasing donor chimerism. Five patients required donor lymphocyte infusions (DLI) during follow-up. One patient received DLI because of persistent B-CLL, despite discontinuing immune suppression at 3 months. Four patients received DLI because of relapse: two of them had indolent lymphoma, one attaining persistent CR and the second achieving stable

disease for two years after DLI. Two patients had transformed lymphomas: one, with a relapse of the indolent component, is now in CR. The other patient relapsed with the aggressive component that remained sensitive to chemotherapy and DLI, although he eventually died of a second aggressive relapse four years later. Only the patient that required DLI for mixed donor chimerism developed GvHD afterwards without an apparent effect on his disease and chimerism status and was eventually retransplanted with a second donor. He died after this second allo-SCT of acute GvHD.

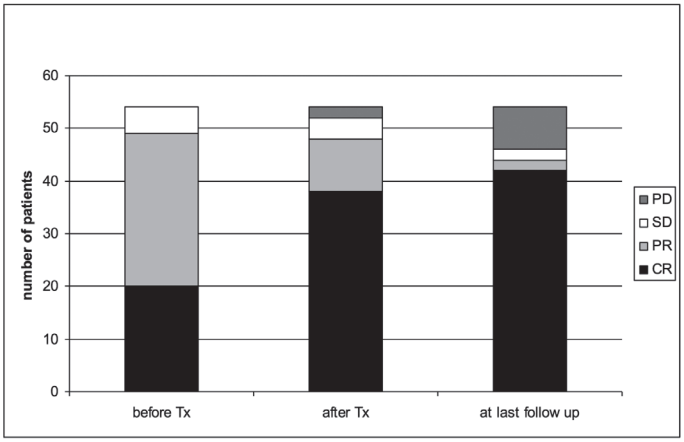

Figure 1: Remission status

PD=progressive disease, SD=stable disease, PR=partial remission, CR=complete remission

Remission status before and after allo-SCT per patient group is shown in Figure 1. After transplant, all patients who were in CR at transplant remained in CR (n=20). An additional 18 patients who were in PR before allo-SCT, attained CR in the first three months after allo-SCT. Three patients with stable disease were in PR immediately after transplant but eventually reached CR and three patients in PR eventually improved to CR, all without DLI. Four patients relapsed within 6 months, and seven relapsed more than 6 months after transplant (range 9-58 months).

Survival

For the entire patient group, 2 year OS was 76% and 4 year OS was 67%, with an EFS of 70% and 66% respectively (see Figure 2). During the follow-up period 18 patients died, six of disease progression, the others of graft versus host disease and/or infections. (Table 1)

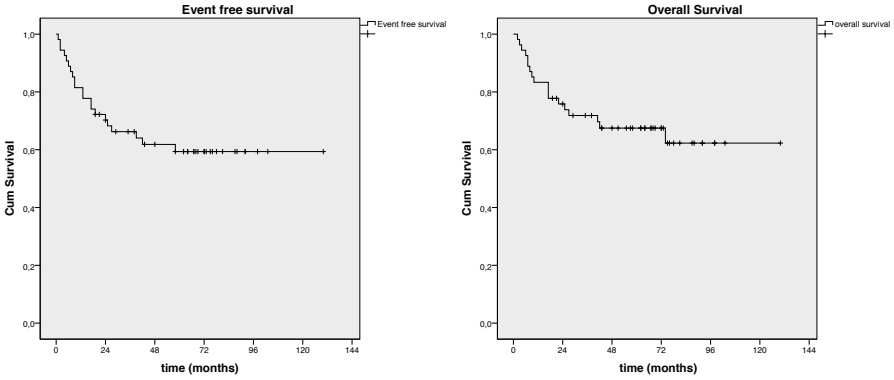

Figure 2 A: event free survival for all patients. B: overall survival for all patients

Analysis per disease category revealed a 4-year OS for B-CLL of 46% (95%CI: 19-73%), 83% for indolent B-cell lymphoma (95%CI: 62-100%), 69% for aggressive lymphoma (95% CI:44-94%) and 74% for transformed lymphoma (95%CI: 52-96%). (NS, p=0.28, see Figure 3)

Four year EFS was 46%, 75%, 55% and 67% respectively (95%CI: 19-73%, 51-100%, 24-87% and 44-91% respectively, NS, p=0.54).

OS was not significantly different between patients with (n=16) or without (n=38) previous auto-SCT. (Figure 4)

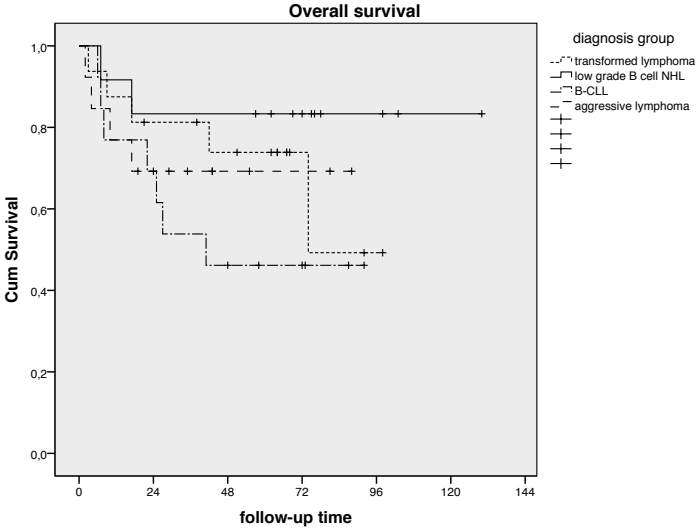

Figure 3: overall survival per disease category

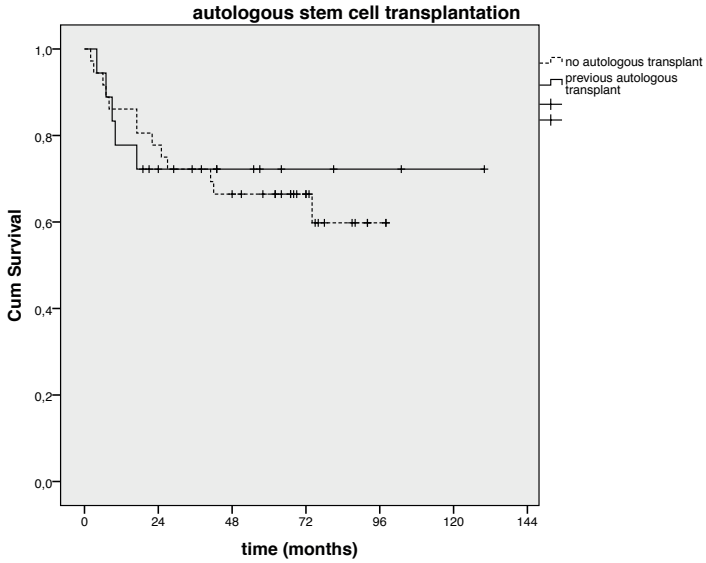

Figure 4: Overall survival in patients with and without previous auto-SCT

Patients who were in CR before allo-SCT had better 4 year OS than patients who were not (77% vs 63%), the difference however being not statistically significant (p=0,47). (Figure 5)

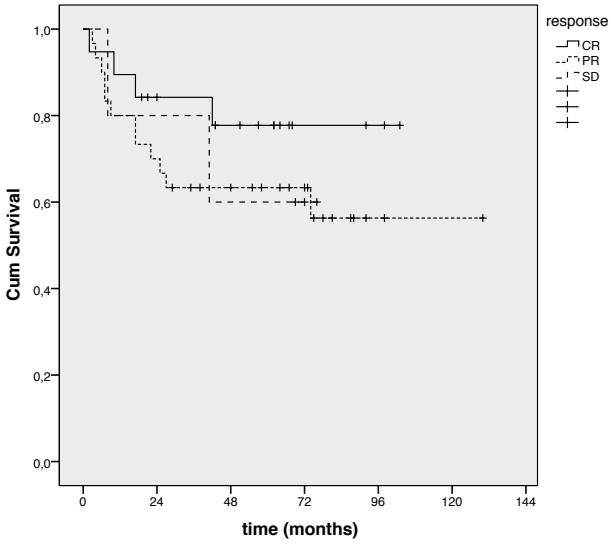

Figure 5: Overall survival and remission status before allo-SCT

Survival or remission status at transplant was not different between the patients who had or had not received rituximab at any time during their treatment. (CR 36% and PR 54% without rituximab versus 34% and 59% with rituximab, respectively)
Patients with only acute GvHD had significantly shorter OS (p=0,003), whereas those with acute GvHD who subsequently developed chronic GvHD did better with similar OS as the patients with only chronic GvHD or no GvHD (Figure 6).

Prognostic factors for survival

Univariate analysis, with the use of a log rank test, identified few variables having prognostic significance for overall survival. Table 2 shows all possible variables with their corresponding p-values. Only acute graft versus host disease was significantly (p=0.046) predictive for worse survival, however this is based on only 6 patients (Figure 6)

Table 2: prognostic factors for survival

		patients	P value
Diagnosis group	B-CLL	13	0.28
	Indolent B cell	12	
	Aggressive NHL	13	
	Transformed NHL	16	
Histologic subtype	B-CLL	12	0.29
	FL	8	
	LPL	4	
	DLBCL	4	
	MCL	4	
	T-NHL	5	
	Richter	1	
	TFL	15	
Age group (years)	24-45	11	0.60
	45-60	25	
	>60	19	
Time diagnosis-transplant	0-5 years	19	0.37
	5-10- years	18	
	10-15 years	5	
Number of previous treatment lines	0-1	4	0.24
	2-3	38	
	>3	12	
Previous auto-SCT	yes	18	0.79
	no	36	
Disease status at transplant	CR	19	0.47
	PR	30	
	SD	5	

Table 2: continued

		patients	P value
CMV mismatch	donor pos, recipient neg	10	0.86
	other	44	
ABO mismatch	major	5	0.17
	minor	8	
	no	41	
Sex mismatch	female to male	15	0.95
	other	29	
GvHD	no GvHD	14	**0.046**
	only acute GvHD	6	
	acute and chronic GvHD	17	
	only chronic GvHD	17	
Previous rituximab	yes	32	0.79
	no	22	

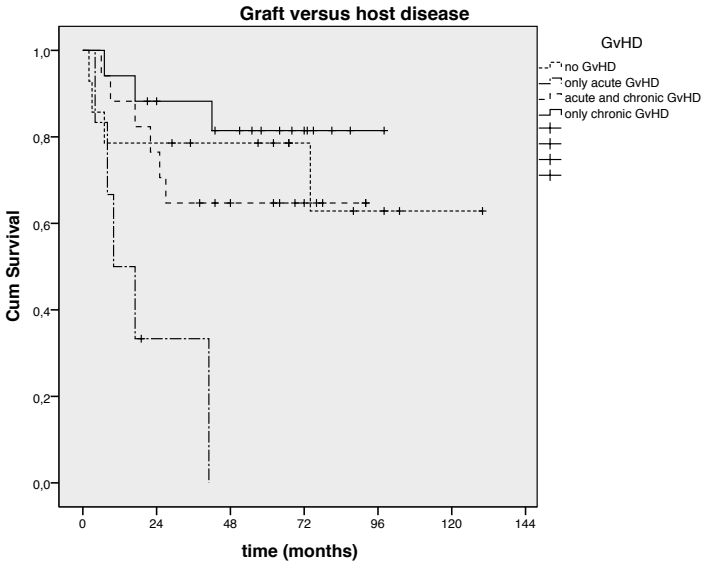

Figure 6: Overall survival and acute and/or chronic GvHD

One year NRM was 11%, increasing to 16% after two years, without any difference between indolent and aggressive lymphoma. (95%CI: 2.2-20% and 5.7-26% respectively)
Four patients died of infectious diseases, of whom three patients used high dose prednisone to treat GvHD.

Graft-versus-host disease

Twenty-three patients (42%) developed acute GvHD after transplantation, of which seven patients had grade I acute GvHD, and 16 patients grade II-IV. 14 patients developed acute GvHD prior to discontinuation of immune suppression, seven needed systemic steroids and seven could be managed with topical steroids only (the latter having all gr1 acute GvHD of the skin). Nine patients developed acute GvHD after discontinuation of immune supression: four after discontinuation of MMF (1-3 weeks after stopping) and 5 after discontinuation of ciclosporin (2-6 weeks, median 3 weeks). All needed systemic GvHD therapy. Four year OS was 72% in the group with grade 1 acute GvHD, and 42% in the group with grade 2-4 acute GvHD needing systemic steroids (p=0,13).

Thirty-four patients (68% of evaluable patients) developed chronic GvHD, of which eight (16%) had limited and 26 (52%) had extensive disease. Two patients developed chronic GvHD before discontinuation of immune suppression and four during reduction of ciclosporin. 22 patients developed chronic GVHD after discontinuation of ciclosporin (median 6 weeks (1 - 40weeks) after stopping). 17 patients had also experienced acute GvHD. Seven patients eventually died because of GvHD (two due to liver GvHD, two of bronchiolitis obliterans syndrome, three of gastro-intestinal GvHD.) At one year post transplant, 45 patients were evaluable, 23 with chronic GvHD. At last follow up, with a median follow up of 6 years, 13 patients were still being treated for chronic GvHD of the 36 patients alive (of whom 25 had suffered from acute and/or chronic GvHD).

Discussion

In this large cohort of homogeneously treated patients with relapsed or refractory B-cell malignancies, with a mean follow up of more than four years, allo-SCT after reduced intensity conditioning with fludarabine and cyclophosphamide proved to be an effective therapy leading to excellent long term survival with acceptable toxicity.

These encouraging survival data may, at least partly, be explained by the fact that only patients with chemosensitive disease were transplanted. Chemoresistance is a known predictor of poor outcome after reduced intensity conditioning (14,15). Secondly, the use of fludarabine-cyclophosphamide as conditioning is effective, as reflected by the evident improvement of remission status in 39% of the patients in the first three months after transplantation while they were still on immunosuppressive therapy. This is important in view of the delayed graft versus lymphoma (GVL) following allo-SCT.

NRM was acceptable with 11% at one year and 16% at two years, without a difference between indolent and aggressive lymphomas. This compares favourably with previously published reports in this patient group. For example: Rezvani et al reported a 3-year NRM for both indolent and aggressive lymphomas of 23% after fludarabine-TBI conditioning. Rodriguez et al found 28% 2 year NRM for the same patient group after fludarabine-melphalan (6,10). Morris et al. reported a 3 year NRM of 11% for indolent lymphomas and 38% for aggressive lymphomas after fludarabine-melphalan-alemtuzumab conditioning (16). Although the number of treatment lines received did not affect survival in our analysis, more intensive pretreatment may have negatively affected NRM in reported series.

In this analysis, survival of 46% at 4 years for CLL patients appeared to be worse as compared to the other malignancies. In contrast, in the series of Sorror, CLL patients did not perform worse than the aggressive lymphomas (17). However, Corradini found in a subanalysis on the FL and CLL patient that overall survival was significantly worse for CLL patients (3yr OS 53% vs 88%), mainly due to a higher relapse risk (3yr 46% vs 14%) (5). This was not seen in our patients, where NRM was the main cause of death (only 1 relapse in 7 patients that died, see table 1)

Patients with indolent lymphoma experienced the best 4-yr overall survival of 83%. Khouri reported similar survival rates of 84% at two years in his group of follicular lymphomas and SLL after conditioning with fludarabine and cyclophosphamide (3). Conflicting data exist as to whether indolent versus aggressive histology impacts upon results after reduced intensity regimens for allo-SCT. In our series, there was no significant difference in outcome between both groups. Corradini found a similar survival for his indolent and aggressive lymphomas (3yr OS 69%) (5). However in the series of Armand et al, indolent histology indeed was a predictor of better OS with 81% as opposed to 42% in the aggressive lymphomas (18). We suggest that reduced intensity allo-SCT should be considered in case of relapsed or refractory aggressive lymphomas since significant long term survival can be achieved, especially in chemosensitive disease.

Survival was not affected by a previous auto-SCT in this analysis, which was also seen in several other series of reduced intensity allo-SCT (19). However, Rodriguez found a significantly worse OS after allo-SCT with reduced intensity conditioning when patients had been treated with auto-SCT before (6). Rezvani reports that patients treated with auto-SCT immediately before allo-SCT did worse. However, this seems to be explained

by the fact that this tandem approach was performed because of their very resistant disease (10). Others found that patients with a short time from auto-SCT to allo-SCT have a higher NRM and lower progression free survival (20). We only included chemosensitive patients and the interval between auto-SCT and allo-SCT was quite long (range 11-96 months, median 38 months). These two facts might be related, since patients relapsing shortly after auto-SCT, often are more refractory to salvage treatment. Our data indicate that if patients respond well to the salvage treatment, previous auto-SCT is not a negative predictor for survival when the interval between transplants is a year or more.

Auto-SCT of DLBCL patients at first relapse, with a cure rate of around 50% in reported series is still considered first choice for these patient catergory (21). Auto-SCT has the benefit of lacking the risk of graft versus host disease, an important cause of morbidity and mortality after allogeneic transplantation, with major impact on the quality of life (22). However, all relapses in the current era occur after previous treatment with rituximab and these patients seem to be more resistant to salvage therapy (23). To avoid increased NRM when allo-SCT is performed shortly after auto-SCT, up-front allo-SCT for this specific patient group may be a valid option. This should preferably be tested in a prospective study, also taking quality of life into consideration.
Our observation that previous rituximab during the remission induction does not add to survival or remission status is most likely explained by the fact that we only transplanted patients with chemosensitive disease. It suggests that having responsive disease is more important than the kind of treatment used to achieve that response.

Studies by the International Bone Marrow Transplant Registry (IBMTR) and the European Group for Blood and Marrow Transplantation (EBMT) have reported that allo-SCT leads to a significantly lower risk of relapse compared with auto-SCT which may relate to the graft-vs-lymphoma-effect (1, 24-26). In our relapsed patients, DLI could be performed in five patients and induced permanent or temporary remissions in four of them. This, and the six additional patients improving their remission after transplant, reaching CR without further therapies, supports the existence of this GVL effect. Moreover, chronic GvHD decreases relapse rate, which can also be attributed to a GVL effect (27). All six patients experiencing improvement of their remission status in the year after transplant suffered from chronic GvHD.

The incidence of acute GvHD (42%) and chronic GvHD (68%) in our patients is similar to reported series of non-T-cell-depleted reduced intensity regimens (3,6,10).

We found that acute GvHD negatively affected survival (fig 6). Although not significant, overall survival seemed worse in patients with grade 2-4 acute GvHD vs grade I GvHD (42% vs 72%, p=0.12). The shorter survival might be explained by the need for systemic steroids early after transplant in more severe acute GvHD with additional risks of severe infections, which indeed occurred in 3 patients. Van Kampen et al. reported similar higher NRM in patients with acute GvHD (20).
The group of patients with long term persistent chronic GvHD in our series was 24% of all patients undergoing allo-SCT. Most studies on allo-SCT report incidence, not long term persistence of GvHD. Analyses of quality of life focus more on long term morbidity and show similar percentages chronically impaired survivors, GvHD having a robust negative relationship with quality of life (22).
The incidence of GvHD, both acute and chronic, is lower when transplanting after T cell depletion, the benefit on survival usually being offset by more infections and a higher relapse rate through abrogation of the GVL effect. Robinson et al. reported 29% acute GVHD after T cell depletion with either ATG or alemtuzumab, versus 58% in recipients of non T cell depleted grafts (14). Morris et al. reported 30% acute GvHD and 6.8% chronic GvHD after alemtuzumab containing reduced intensity conditioning. Eventual 3 year OS was only 35% for high grade lymphoma (8/37 refractory disease) and 73% for low grade lymphoma (1/41 refractory) (16). It could be argued whether the increased risk of relapse is counterbalanced by the gain of less toxicity.

In conclusion, reduced intensity conditioning with fludarabine cyclophosphamide is a feasible scheme with acceptable toxicity and proven long term efficacy. It is effective for both indolent and aggressive lymphoid malignancies, even after previous auto-SCT, provided patients are sensitive to re-induction therapy. Due to the excellent anti-lymphoma activity, the fludarabine-cyclophosphamide regimen deepens responses after allo-SCT, allowing time for the development of a graft versus lymphoma effect.

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